# PDL DRUG REVIEW

## Proprietary Name: Zepbound®
## Common Name: tirzepatide
## PDL Category: Endocrine Metabolic Agents

**Pharmacology/Usage:** Tirzepatide, the active ingredient of Zepbound®, is a glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist. It contains a C20 fatty diacid that enables albumin binding and prolongs the half-life. Tirzepatide selectively binds to and activates both the GIP and GLP-1 receptors, the targets for native GIP and GLP-1. GLP-1 in a physiological regulator of appetite and caloric intake. Nonclinical studies suggest the addition of GIP may further contribute to the regulation of food intake.

Both GIP receptors and GLP-1 receptors are found in areas of the brain involved in appetite and energy expenditure regulation. Animal studies demonstrate that tirzepatide distributes to and activates neurons in brain regions involved in regulation of appetite and food intake.

This NDR will focus on Zepbound's treatment indication of moderate to severe OSA.

**Indication:** In combination with a reduced-calorie diet and increased physical activity:

- To reduce excess body weight and maintain weight reduction long term in adults with obesity or adults with overweight in the presence of at least one weight-related comorbid condition.
- To treat moderate to severe obstructive sleep apnea (OSA) in adults with obesity.

A limitation of use includes that Zepbound® contains tirzepatide. Co-administration with other tirzepatide-containing products or with any glucagon-like peptide-1 (GLP-1) receptor agonist is not recommended.

There is no pregnancy category for this medication; however, the risk summary indicates that weight loss offers no benefit to a pregnant patient and may cause fetal harm. Advise pregnant patients that weight loss is not recommended during pregnancy and to discontinue Zepbound® when a pregnancy is recognized. Available data with use in pregnant patients are not sufficient to assess for a drug-related risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Per animal reproduction studies, there may be risks to the fetus from exposure to tirzepatide during pregnancy. There will be a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to tirzepatide during pregnancy. Pregnant patients exposed to Zepbound® and healthcare providers are encouraged to contact Eli Lilly and Company at 1-800-545-5979. The safety and efficacy of use in the pediatric population have not been established.

**Dosage Form:** Solution in pre-filled single-dose pens or single-dose vials for Injection, available as:

- 2.5mg/0.5ml.
- 5mg/0.5ml.
- 7.5mg/0.5ml.
- 10mg/0.5ml.
- 12.5mg/0.5ml.
- 15mg/0.5ml.

**Recommended Dosage:** The following are important administration instructions:

- Prior to initiation of Zepbound®, train patients and caregivers on proper injection technique.

- Instruct patients using the single-dose vial to use a syringe appropriate for dose administration.
- Administer Zepbound® in combination with a reduced-calorie diet and increased physical activity.
- Administer Zepbound® once weekly at any time of the day, with or without meals.
- Inject subcutaneously (SC) in the abdomen, thigh, or upper arm. Rotate injection sites with each dose.

The following is recommended dose escalation schedule and maintenance information:

- The recommended starting dosage for all indications is 2.5mg injected SC once weekly (QW) for 4 weeks.
- The 2.5mg dose is for treatment initiation and is not approved as a maintenance dosage.
- The dosage escalation should be followed to reduce the risk of GI adverse reactions.
- After 4 weeks, increase the dosage to 5mg injected SC QW. The dosage may be increased in 2.5mg increments, after at least 4 weeks on the current dose.
- Consider treatment response and tolerability when selecting the maintenance dosage. If patients do not tolerate a maintenance dosage, consider a lower maintenance dosage.
- The recommended maintenance dosage for OSA is 10mg or 15mg SC QW.
- The maximum Zepbound® dosage for all indications is 15mg SC QW.

If a dose is missed, administer Zepbound® as soon as possible within 4 days (96 hours) after the missed dose. If more than 4 days have passed, skip the missed dose and administer the next dose on the regularly scheduled day. In each case, patients can then resume their regular, once weekly dosing schedule.

The day of weekly administration can be changed, if necessary, as long as the time between the two doses is at least 3 days (72 hours).

No dosage adjustment is recommended for patients with renal impairment. Monitor renal function in patients reporting adverse reactions to Zepbound® that could lead to volume depletion. No dosage adjustment is recommended for patients with hepatic impairment.

**Drug Interactions:** Zepbound® lowers blood glucose. When starting Zepbound®, consider reducing the dose of concomitantly administered insulin or insulin secretagogues (e.g., sulfonylureas) to reduce the risk of hypoglycemia.

Zepbound® delays gastric emptying and thus has the potential to impact the absorption of concomitantly administered oral medications. Use caution when oral medications are administered concomitantly with Zepbound®.

Monitor patients on oral medications dependent on threshold concentrations for efficacy and those with a narrow therapeutic index (e.g., warfarin) when concomitantly administered with Zepbound®.

Advise patients using oral hormonal contraceptives to switch to a non-oral contraceptive method, or add a barrier method of contraception, for 4 weeks after initiation with Zepbound® and for 4 weeks after each dose escalation. Hormonal contraceptives that are not administered orally should not be affected.

**Box Warning:** Zepbound® has a box warning regarding the risk of thyroid C-cell tumors.

- In rats, tirzepatide causes dose-dependent and treatment duration-dependent thyroid C-cell tumors at clinically relevant exposures. It is not known whether Zepbound® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of tirzepatide-induced rodent thyroid C-cell tumors has not been determined.
- Zepbound® is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk for MTC with the use of Zepbound® and inform them of symptoms of thyroid tumors. Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with Zepbound®.

**Common Adverse Drug Reactions:** *Listed % incidence for adverse drug reactions= reported % incidence for drug (Zepbound® 10mg) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included nausea (21%), diarrhea (13%), vomiting (9%), constipation (9%), abdominal pain (4%), dyspepsia (5%), injection site reactions (6%), fatigue (3%), hypersensitivity reactions (2%), eructation (4%), hair loss (3%), gastroesophageal reflux disease (2%), flatulence (1%), abdominal distension (1%), dizziness (3%), and hypotension (1%).

Use of Zepbound® has been associated with GI adverse reactions, sometimes severe. Zepbound® has not been studied in patients with severe GI disease, including severe gastroparesis, and is therefore not recommended in these patients.

Use of Zepbound® has been associated with acute kidney injury, which can result from dehydration due to GI adverse reactions to Zepbound®. In patients treated with GLP-1 receptor agonists, there have been post marketing reports of acute kidney injury and worsening of chronic renal failure, which may sometimes require hemodialysis. Some of these events have been reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. Monitor renal function in patients reporting adverse reactions to Zepbound® that could lead to volume depletion.

Treatment with Zepbound® and GLP-1 receptor agonists is associated with an increased occurrence of acute gallbladder disease. If cholecystitis is suspected, gallbladder diagnostic studies and appropriate clinical follow-up are indicated.

Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with GLP-1 receptor agonists or tirzepatide. After starting Zepbound®, observe patients for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting). If pancreatitis is suspected, discontinue Zepbound® and start appropriate management. Continuation of Zepbound® after a confirmed diagnosis of pancreatitis should be individually determined in the clinical judgment of a patients' health care provider.

There have been post marketing reports of serious hypersensitivity reactions in patients treated with tirzepatide. If hypersensitivity reactions occur, advise patients to seek medical attention and discontinue Zepbound®. Do not use in patients with a previous serious hypersensitivity reaction to tirzepatide or any of the excipients in Zepbound®. Serious hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with GLP-1 receptor agonists. Use caution in patients with a history of angioedema or anaphylaxis with a GLP-1 receptor agonist because it is not known whether such patients will be predisposed to these reactions with Zepbound®.

Zepbound® lowers blood glucose and can cause hypoglycemia. Hypoglycemia has also been associated with Zepbound® and GLP-1 receptor agonists in adults without type 2 diabetes mellitus (DM). Inform patients of the risk of hypoglycemia and educate patients on the signs and symptoms of hypoglycemia. In patients with DM, monitor blood glucose prior to starting Zepbound® and during Zepbound® treatment. The risk of hypoglycemia may be lowered by a reduction in the dose of insulin or sulfonylurea.

Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. Tirzepatide has not been studied in patients with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy, or diabetic macular edema. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy.

Suicidal behavior and ideation have been reported in clinical trials with other weight management products. Monitor patients treated with Zepbound® for the emergence or worsening of depression, suicidal thoughts or behaviors,

and/or any unusual changes in mood or behavior. Discontinue Zepbound® in patients who experience suicidal thoughts or behaviors and avoid Zepbound® in patients with a history of suicidal attempts or active suicidal ideation.

Zepbound® delays gastric emptying. There have been rare post marketing reports of pulmonary aspiration in patients receiving GLP-1 receptor agonists undergoing elective surgeries or procedures needing general anesthesia or deep sedation who had residual gastric contents despite reported adherence to preoperative fasting recommendations. Available data are not sufficient to inform recommendations to mitigate the risk of pulmonary aspiration during general anesthesia or deep sedation in patients taking Zepbound®. Instruct patients to inform healthcare providers prior to any planned surgeries or procedures if they are taking Zepbound®.

**Contraindications:** In patients with:

- A personal or family history of MTC or in patients with MEN 2.
- Known serious hypersensitivity to tirzepatide or to any of the excipients of the product.

**Manufacturer:** Eli Lilly and Company

**Analysis:** As this review is to focus on the OSA indication, this analysis section will only include the studies for this specific indication.

The efficacy of Zepbound® for moderate to severe OSA (apnea-hypopnea index [AHI] ≥15) in patients with obesity (BMI ≥30kg/$m^2$) was assessed in a master protocol clinical trial that included two randomized, double-blind, placebo-controlled trials (Study 5 and Study 6) of 52 weeks duration that enrolled adult patients (N=469). In both studies, patients were randomized to receive Zepbound® or placebo and all patients received instruction on a reduced-calorie diet and increased physical activity counseling throughout the study. Patients with type 2 DM were excluded.

Study 5 included adult patients (N=234) with moderate to severe OSA and obesity who were unable or unwilling to use Positive Airway Pressure (PAP) therapy. Included patients had a mean age of 48 years (range 20 to 76), while 67% were male and 66% were white. Study 6 included adult patients (N=235) with moderate to severe OSA and obesity who were on PAP therapy. Included patients had a mean age of 52 years (range 26 to 79), while 72% were male and 73% were white. The baseline mean BMI (kg/$m^2$) was 39.1 in study 5 and 38.7 in Study 6, while 75.6% and 77.4% respectively had hypertension, 10.3% and 11.1% respectively had cardiac disorders, and 80.8% and 83.8% respectively had dyslipidemia. The mean baseline AHI (events/hour) was 51.5 in study 5 and 49.5 in study 6.

The primary endpoint for both studies was the change from baseline in the AHI at week 52. Patients in Study 5 were unable or unwilling to use PAP therapy, while patients in Study 6 were on PAP therapy and instructed to suspend PAP for 7 days prior to assessment of the primary endpoint. The clinical studies for OSA did not assess the timing or appropriateness of PAP discontinuation in patients who were previously compliant with PAP therapy.

In Studies 5 and 6, Zepbound® treatment for 52 weeks resulted in a statistically significant reduction in AHI compared with placebo, and greater proportions of patients treated with Zepbound® achieved remission or mild non-symptomatic OSA compared to placebo. The table below, adapted from the prescribing information, presents the information. Note that in both studies, patients treated with Zepbound® achieved a greater reduction in systolic blood pressure and high-sensitivity C-reactive protein levels compared to placebo.

| | Study 5 | | Study 6 | |
|---|---|---|---|---|
| | Placebo (N=120) | Zepbound® [1] (N=114) | Placebo (N=114) | Zepbound® [1] (N=119) |
| **AHI (events/hr)** | | | | |
| Baseline mean | 50.1 | 52.9 | 53.1 | 46.1 |

| | Study 5 | | Study 6 | |
|---|---|---|---|---|
| | Placebo (N=120) | Zepbound® [1] (N=114) | Placebo (N=114) | Zepbound® [1] (N=119) |
| Change from baseline | -5.3 | -25.3 | -5.5 | -29.3 |
| Difference from placebo; p-value | -20; p<0.001 | | -23.8; p<0.001 | |
| **% Change in AHI** | | | | |
| % change from baseline | -3 | -50.7 | -2.5 | -58.7 |
| % difference from placebo; p-value | -47.7; p<0.001 | | -56.2; p<0.001 | |
| **% of patients with ≥50% reduction in AHI** | | | | |
| % of patients with ≥50% reduction in AHI | 19 | 61.2 | 23.3 | 72.4 |
| % difference from placebo; p-value | 42.8; p<0.001 | | 48.6; p<0.001 | |
| **Remission or mild non-symptomatic OSA** | | | | |
| % of patients with AHI <5 or AHI 5-14 and Epworth Sleepiness Scale ≤10 | 15.9 | 42.2 | 14.3 | 50.2 |
| % difference from placebo; p-value | 28.7; p<0.001 | | 33.2; p<0.001 | |
| **Sleep apnea-specific hypoxic burden (% min/h)** | | | | |
| Baseline mean | 137.8 | 153.6 | 142.1 | 132.2 |
| Change from baseline | -25.1 | -95.2 | -41.7 | -103 |
| Difference from placebo; p-value | -70.1; p<0.001 | | -61.3; p<0.001 | |
| **Body weight (kg)** | | | | |
| Baseline mean | 112.8 | 116.7 | 115.1 | 115.8 |
| % change from baseline | -1.6 | -17.7 | -2.3 | -19.6 |
| % difference from placebo; p-value | -16.1; p<0.001 | | -17.3; p<0.001 | |

[1] 10mg or 15mg

In OSA clinical studies, Zepbound®-treated patients demonstrated improvement in sleep-related impairment compared to those who were treated with placebo. Sleep-related impairment was assessed using the Patient-Reported Outcomes Measurement Information System (PROMIS) Short Form Sleep-Related Impairment 8a.

**Place in Therapy:** Zepbound® is a glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist indicated in combination with a reduced-calorie diet and increased physical activity to: reduce excess body weight and maintain weight reduction long term in adults with obesity or adults with overweight in the presence of at least one weight-related comorbid condition, as well as to treat moderate to severe obstructive sleep apnea (OSA) in adults with obesity. A limitation of use includes that coadministration with other tirzepatide-containing products or with any GLP-1 receptor agonist is not recommended. The backbone of treatment for adults with OSA and an AHI ≥15 events per hour of sleep is positive airway pressure (PAP) therapy.[2]

Zepbound® does have a box warning regarding risk of thyroid c-cell tumors. The efficacy of Zepbound® for OSA was assessed in two randomized, double-blind, placebo-controlled trials that included patients with moderate to severe OSA (apnea-hypopnea index [AHI] ≥15) with obesity (BMI ≥30kg/m$^2$). The primary endpoint for both studies was the change from baseline in AHI at week 52, and results suggested that treatment with Zepbound® for 52 weeks resulted in a statistically significant reduction in AHI as compared with placebo.

## Summary

It is recommended that Zepbound® should be non-preferred in order to confirm the appropriate diagnosis and clinical parameters for use.

**PDL Placement:**
- ☐ **Preferred**
- ☒ **Non-Preferred with Conditions**

## References

[1] Zepbound® [package insert]. Indianapolis, IN: Lilly USA, LLC; 2024.
[2] UpToDate. Obstructive sleep apnea: Overview of management in adults. Accessed February 2025.